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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/676,834	09/29/2000	Michael Z. Gilman	APBI-P04-340	4232

28120 7590 06/10/2003

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EXAMINER	
SANDALS, WILLIAM O	

ART UNIT	PAPER NUMBER
1636	17

DATE MAILED: 06/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/676,834	Applicant(s) Gilman
	Examiner William Sandals	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Feb 13, 2003*

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 5-14, and 16-38* is/are pending in the application.

4a) Of the above, claim(s) *6-13, 16, and 21-23* is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 14, 17-20, and 24-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

1. Claims 1-3, 5-14 and 16-38 are pending. Claims 6-13, 16 and 21-23 have been withdrawn by previous election of Group II in Paper No. 12, filed June 24, 2002. Claims 4 and 15 are cancelled by amendment in Paper No. 16, filed February 13, 2003.

2. The rejection of claims 1-5, 14, 15 and 17-20 under 35 U.S.C. 112, first paragraph, written description, in the previous office action has been overcome by amendment and the rejection is withdrawn. Applicant's arguments presented in Paper No. 16, pages 13-15, regarding the rejections are moot in view of the amendments.

3. The rejection of claims 14, 15, 18-20 and 24-38 under 35 U.S.C. 112, first paragraph, scope of enablement, in the previous office action has been overcome by Applicant's arguments presented in Paper No. 16 at pages 15-16, and the rejection is withdrawn.

4. The rejection of claims 1-5, 14, 15, 17-20 and 24-38 under 35 U.S.C. 112, second paragraph in the previous office action has been overcome by amendment and the rejection is withdrawn. Applicant's arguments presented in Paper No. 16 at pages 16-17, regarding the rejections are moot in view of the amendments.

5. The rejection of claims 1-5, 14, 15, 71-20 and 24-38 under 35 U.S.C. 102(e) as being anticipated by US 5,654,168 in the previous office action has been overcome by amendment and

the rejection is withdrawn. Applicant's arguments presented in Paper No. 16 at pages 17-18, regarding the rejections are moot in view of the amendments.

6. The rejection of claims 1-5, 14, 15, 17-20 and 24-38 under 35 U.S.C. 103(a) as being unpatentable over US 5,654,168 in view of WO 94/18317 in the previous office action has been overcome by amendment and the rejection is withdrawn. Applicant's arguments presented in Paper No. 16 at pages 17-18, regarding the rejections are moot in view of the amendments.

7. New grounds of rejection are presented below.

8. Claim 5 is rejected under 35 U.S.C. 112, second paragraph.

9. Claims 1-3, 5, 14, 17-20 and 24-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,654,168 (Bujard et al., of record) in view of US 5,639,725 (O'Reilly et al.), and further in view of WO 94/18317 (Crabtree et al., of record).

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 5 recites the limitation "The engineered cell" in line 1. There is insufficient antecedent basis for this limitation in the claim. Deleting "engineered" would correct this defect.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1, 3, 5, 14, 17, 18, 20 and 24-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,654,168 (Bujard et al., of record) in view of US 5,639,725 (O'Reilly et al.).

15. The claims are drawn to a cell containing a first (or pair of) genetic construct(s) encoding chimeric proteins. The chimeric proteins comprise at least one ligand-binding domain (LBD) which can bind a selected ligand and a second protein domain which is heterologous with respect to the ligand-binding domain as recited in claim 1. The ligand may be an antibiotic. The cell also contains a target gene encoding angiostatin. The expression of the angiostatin gene is under

the control of a transcriptional control element which is responsive to binding of the ligand to the ligand-binding domain, wherein transcription of the angiostatin gene is regulated in a manner dependent upon the expression of the chimeric protein and upon the presence of the ligand. The angiostatin gene may encode an angiostatin protein of human origin, as recited in claim 5. The construct may be used in a method of rendering a cell capable of ligand-regulatable expression of the angiostatin gene by introducing the above construct and the angiostatin gene into the cell, as recited in claim 14. The cell may be in vitro or in a host organism (claims 18 and 26-28). The construct and the angiostatin gene may be introduced into a cell by a viral vector (claims 24-25). The construct may further comprise one or more selectable markers (claims 29-30). The ligand may have various binding Kd's. The ligand may be less than 5 Kd, may be orally active and may be membrane permeable (claims 32-34 and 37-38). There may be two or more LBD's, and the LBD may be from 50-350 amino acids in length (claims 35-36).

Bujard et al. teaches an inducible regulatory system for control of transcription comprising (see especially the summary, columns 9-15, 18, 19, 27 and 29) a genetic construct encoding a chimeric protein, which is useful for the regulation of transcription of a target gene, and a construct encoding the target gene. The chimeric protein consists of a ligand binding domain and a heterologous domain which binds to the transactivation domain of a target gene. The chimeric protein is expressed in a cell. The chimeric protein binds to a ligand (antibiotic). Upon ligand binding to the chimeric protein, the chimeric protein binds to a transactivating region on a target gene thereby regulating the expression of the target gene, which may be an

anti-angiogenesis factor (see col. 29, lines 26-55). The regulation may be performed in a host organism which may be a human (see col. 27, lines 28-46). The genetic construct and the target gene may be introduced into the cell by a viral vector (see cols. 11-12 and col. 14, line 61-col. 15, line 17). Numerous cell types are described (see col. 13, lines 53-64). Selectable markers may be used (see col. 14, lines 29-53). Claimed Kd values and molecular size is taught (see col. 26, bottom). The ligand binding domain is contained in a 207 amino acid protein (see column 6, line 16-column 9, line 26). The regulation of the transcription of the target gene is controlled by the presence or absence of the antibiotic ligand, thereby inducibly regulating the transcription of the desired target (anti-angiogenesis) gene.

Bujard et al. does not teach that the anti-angiogenesis factor (col. 29, lines 26-55) is the angiostatin gene.

O'Reilly et al. teach the angiostatin protein at the abstract and throughout the specification, which is an anti-angiogenesis factor useful for instance in inhibiting angiogenesis in tumor growth. O'Reilly teaches at the summary and columns 6-10, the transcription and expression of an angiostatin gene in vitro and in vivo. O'Reilly teaches at column 9, the desirable and useful expression of the angiostatin gene in an appropriate vector for inhibition of undesired and uncontrolled angiogenesis, such as occurs in cancer and tumors. O'Reilly et al. teach at columns 3 and 4 that tumor growth is dependent upon angiogenesis, and that angiogenesis is essential and desirable for wound healing, and for fetal and embryonal development for example. It is therefore desirable to inhibit angiogenesis in a specific and

controlled manner. Angiostatin is taught to be useful for inhibition of angiogenesis with minimal side effects (see column 5).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to inducibly control the expression of angiostatin by modifying the target gene encoding an anti-angiogenesis factor taught by Bujard et al. by using the gene encoding angiostatin (an anti-angiogenesis factor) of O'Reilly et al. for the expected benefit of expressing the angiostatin gene in a controlled manner to specifically inhibit unwanted angiogenesis, especially angiogenesis related to tumor growth, with minimal side effects. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Bujard et. al. and O'Reilly et. al. who demonstrate the expression of an anti-angiogenesis factor in cells in vitro and in vivo.

16. Claims 1-3, 5, 14, 17-20 and 24-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et. al. and O'Reilly et. al. as applied to claims 1, 3, 5, 14, 17, 18, 20 and 24-38 above, and further in view of WO 94/18317 (Crabtree et al., of record).

The claims are drawn to the invention as described above, and where the transcription of the angiostatin gene may be responsive to dimerization of the chimeric protein (claims 2 and 19), and where the LBD may be an immunophilin ligand binding domain, a cyclophilin ligand binding domain or a steroid receptor binding domain, as recited in claims 2, 3, 19 and 20.

Bujard et. al. and O'Reilly et. al. teach the invention as described above.

Bujard et. al. and O'Reilly et. al. do not teach that the transcription of the angiostatin gene may be responsive to dimerization of the chimeric protein in the presence of the ligand, nor that the LBD may be an immunophilin ligand binding domain, a cyclophilin ligand binding domain or a steroid receptor binding domain.

Crabtree et al. teach (see especially pages 6-7) the equivalence of an antibiotic binding domain, a cyclophilin ligand binding domain or a steroid binding domain to practice a method of the invention. Crabtree et al. teach a method of regulating expression of a target gene by exposing a cell to a ligand. The cell is transfected with a genetic construct encoding a chimeric protein comprising a ligand binding domain and a second domain, and which is also transfected with a target gene that is transcriptionally responsive to the chimeric protein when the chimeric protein is bound to a ligand. The ligand binds to ligand binding domains in chimeric proteins expressed from the genetic constructs. While the ligand is bound to the ligand binding domains of the chimeric proteins, the ligand-chimeric protein complex binds to a transactivating region operatively linked to the target gene. The binding of the ligand-chimeric proteins complex to the transactivating region of the target gene regulates the expression of the target gene, both in vitro and in vivo. The ligand-bound chimeric proteins may dimerize or multimerize to effect the regulation of the target gene. Crabtree et al. teach at pages 12-16, that there are multiple types of expression regulation chimeric proteins available to one of ordinary skill in the art, and that each type of expression regulating chimeric protein may operate in a dimerized or multimerized manner. Each type of chimeric regulating protein may be bound by a unique ligand. Each

ligand/chimeric protein combination may be used to regulate a desired target gene in a specific cell or cellular compartment. Dimerization or multimerization also results in higher binding affinity of the chimeric protein for its responsive sequence in the target gene (see page 30, lines 15-33).

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to modify the ligand-binding of the chimeric protein, which induces expression of the desired anti-angiogenesis factor as taught by Bujard et al. with the ligand binding which induces dimerizing and multimerizing of the chimeric protein, where the dimerized or multimerized chimeric protein induces expression of the desired gene as taught by Crabtree et al. for the expected benefit of expressing the angiostatin gene to inhibit angiogenesis using different ligands to bind chimeric regulating proteins, in different cell types or cellular compartments with higher affinity for the responsive sequence in the desired target gene as taught by Crabtree et al. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Bujard et. al., O'Reilly et. al. and Crabtree et al. who demonstrate the regulation of expression of a target gene in cells in vitro and in vivo.

Conclusion

17. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61

(November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Tech Center customer service center at telephone number (703) 308-0198.

William Sandals, Ph.D.
Examiner
May 9, 2003

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